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CLAIM 1-2 (ORIGINAL)

1. Compounds or their salts having the following general formulas (I) and (II):

$$A—B_{bo}—C\cdot N(O)_s \qquad (I)$$

wherein:

s = is an integer equal to 1 or 2, preferably s = 3;

bo = 0 or 1;

A = R—T_1-, wherein

R is the drug radical and

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -T_B—X_2—T_{B1}- wherein

T_B and T_{B1} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

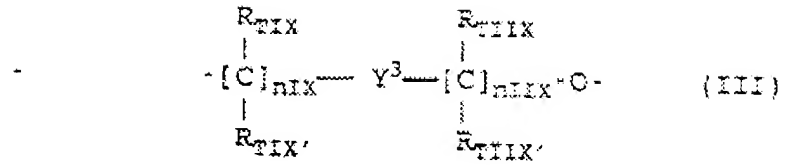
T_{B1} = $(CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0, and tx = 0 when txx = 1; X is as above defined;

X_2 is a bivalent bridging bond as defined below;

C is the bivalent -T_C-Y- radical, wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is:



(III)

wherein:

nIX is an integer between 0 and 3, preferably 1;

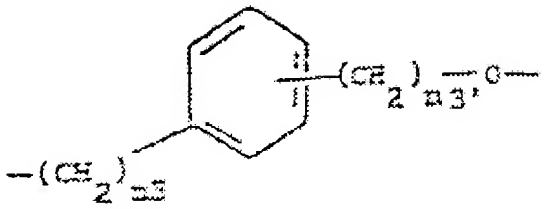
nIIX is an integer between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

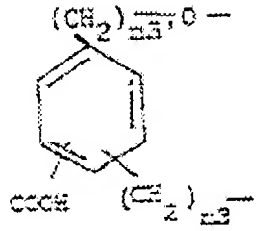
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms.

or Y is Y_0, selected from the following:

an alkylenoxy group R'O wherein R' is linear or when possible branched C_1-C_{20}, preferably having from 1 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be replaced by heteroatoms, the ring can have side chains of R' type, R' being as above defined; or



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



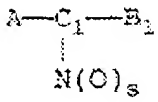
wherein n3 and n3' have the above mentioned meaning

wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4;

preferably Y = -R'O- wherein R' is as above defined;

preferably R' is a C_1-C_6 alkyl;



(II)

wherein:

C_1 = $-T_{CI}-Y'(-T_{CII}-)$

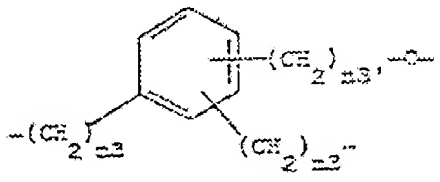
wherein T_{CI} and T_{CII} are equal or different,

T_{CI}= (CO) when t = 0, T_{CI} = X when t' = 0, X being as above defined;

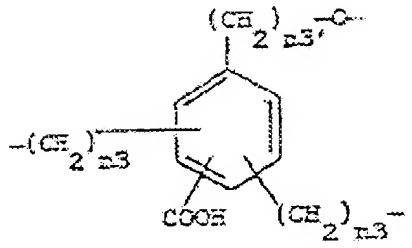
T_{CII}= $(CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that tI = 1 when tII = 0, and tI = 0 when tII = 1; X is as above defined;

Y' is as Y above defined, but with three free valences insterad of two, preferably:

- a -R'O- group wherein R' is as above defined, preferably an alkyl from 2 to 6 carbon atoms, or

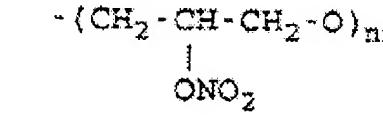


wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

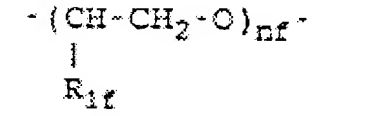


wherein n3 and n3' have the above mentioned meaning;

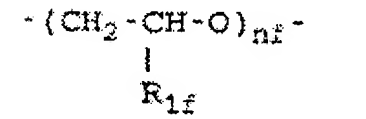
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



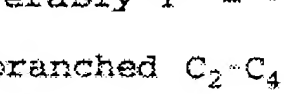
wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably Y' =  wherein R' is a linear or branched C_2-C_4, the oxygen which in Y' is covalently linked to the $-N(O)_s$ group is at the

end of the free bond indicated in the formula of C_1;

B_1 = $-T_{BII}—X_{2a}$

wherein X_{2a} is a monovalent radical as defined below, T_{BII} = (CO) when tI = 0, T_{BII} = X when tII = 0, X being as above defined;

- X_2, bivalent radical is such that the corresponding precursor of B: $-T_B—X_2—T_{BI}$ meets test 5 but not test 4, precursor in which the T_B and T_{BI} free valences are each saturated with -OZ, -Z, or with $-Z^I-N-Z^{II}$,
  Z^I and Z^{II} being equal or different and have the Z values as defined below, depending on whether T_B and/or T_{BI} = CO or X, in connection with the values of t, t', tx and txx;
- the precursor of C when b0 = 0 is of $-T_C-Y-H$ type wherein the T_C free valence is saturated with -OZ, -Z, or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being as above defined, meets test 5;
- X_{2a} monovalent radical, such that the corresponding precursor of B_1 $-T_{BII}—X_{2a}$ meets test 5 but not test 4, precursor wherein the T_{BII} free valence is

saturated with -OZ, -Z or with $-Z^{I}-\underset{|}{N}-Z^{II}$, $-Z^{I}$ and Z^{II} being equal or different and having the Z values as defined below, depending on whether T_{BII} = CO or X, in connection with the tI and tII values;

the drug A = R—T_1-, wherein the free valence is

saturated as indicated hereinafter:

- when t' = O with:
  - O-Z wherein Z = H or R_{1a}, R_{1a} being a linear or branched when possible C_3-C_{10} alkyl, preferably C_1-C_5, or with
  - Z^{I}-N-Z^{II}, Z^{I} and Z^{II} being as above defined;
- when t = 0 with -Z, wherein Z is as above defined, with the proviso that the drug is not a steroid,

is such as to meet at least one of tests 1-3;

wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula A = R-T_1· wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by

the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies

with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis

(cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

wherein test 3 (L-NAME) is a test in vivo

carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N-ω-nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrified, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric

tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages

(determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

wherein test 4, which must not be met by the precursors of B or B_1 with the free valences saturated as above defined, is the following: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B_1 at a 10^{-4} M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is

calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance

values of the solution containing the test compound + DPPH and that of the solution containing only DPPH. The criterium for acceptance of the compounds according to this test is the following: test 4 is met by precursor compounds if the inhibition percentage as above defined is higher than or equal to 50%; the precursor of B or B_1 must not meet test 4;

wherein test 5 is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B_1 or of C = -T_C-Y-H, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $Fe^{II}(NH_4)_2(SO_4)_2$; after having thermostatted the solution at 37°C for one hour, are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the solutions is then read at

532 nm; the inhibition induced by the precursor of B or B_1 or C = $-T_c-Y-H$ in the confront of radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B_1 or C = $-T_c-Y-H$ is higher than or equal to 50%;

provided that in the compounds of formula (I) the following drugs under the following conditions are excluded:

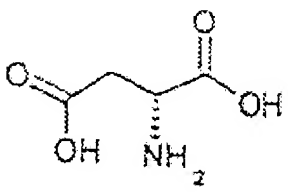
- when bo = 0 and C = $-T_c-Y_0-$, wherein the free valence of Y_0 is saturated as above indicated, s = 2, the drug of formula A = R—T_1-, as above defined, has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE-inhibitors), prostaglandins;

- when bo = 0 and C = -T_c-Y-, wherein the free valence of Y is saturated as above indicated, and s = 2, the drugs of formula A = R—T_1- belonging to the class of non steroid antiinflammatory drugs.

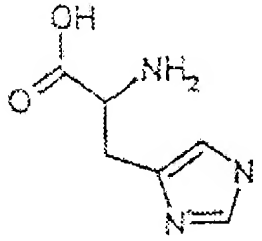
2. Compounds according to claim 1 wherein the precursor compound of B or B_1 is selected from the following compounds:

- Aminoacids: aspartic acid (PI), histidine (PII),

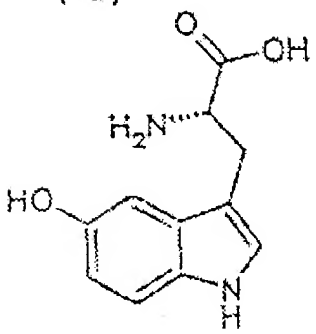
5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



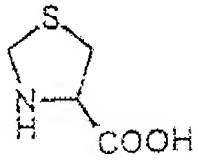
(PI)



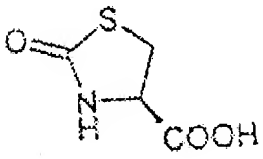
(PII)



(PIII)



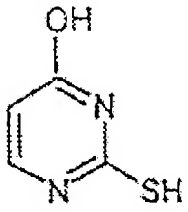
(PIV)



(PV)

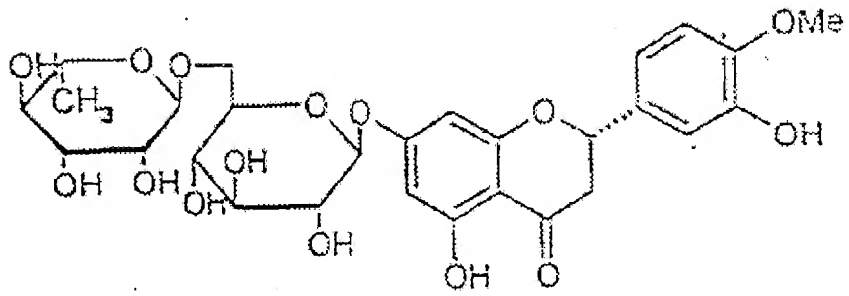
- mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1-α-OH vitamin D2 (QV),

flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1α-hydroxyvitamin D2 (QX) the compound derived from 1α,25-dihydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)

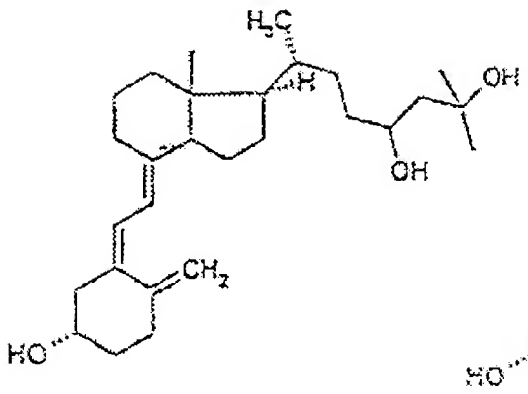


(QI)

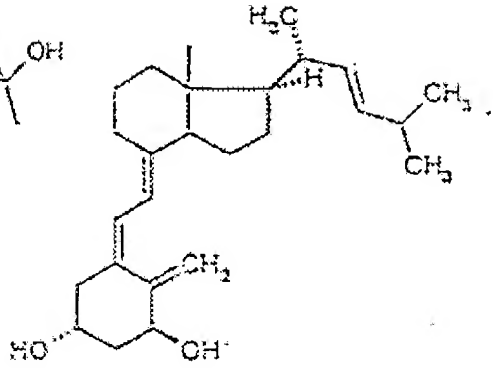
(QII)



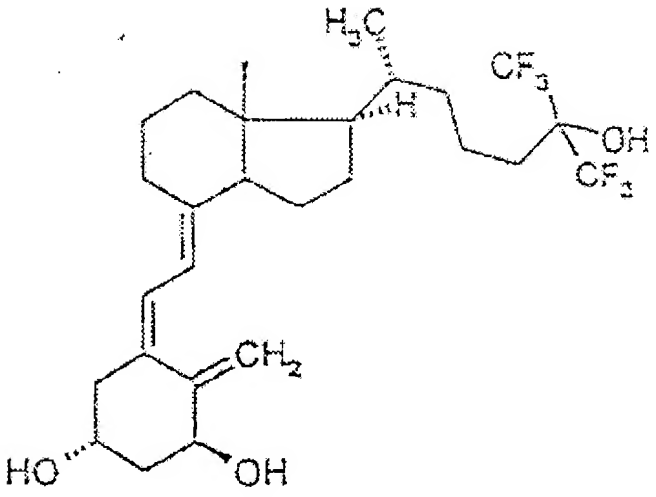
(QIII)



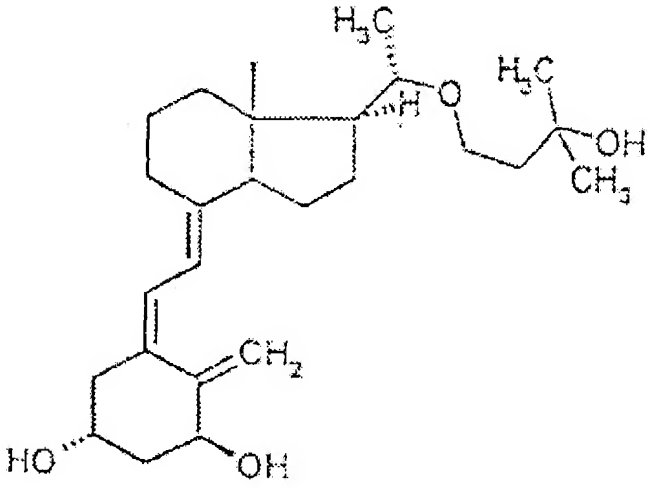
(QIV)



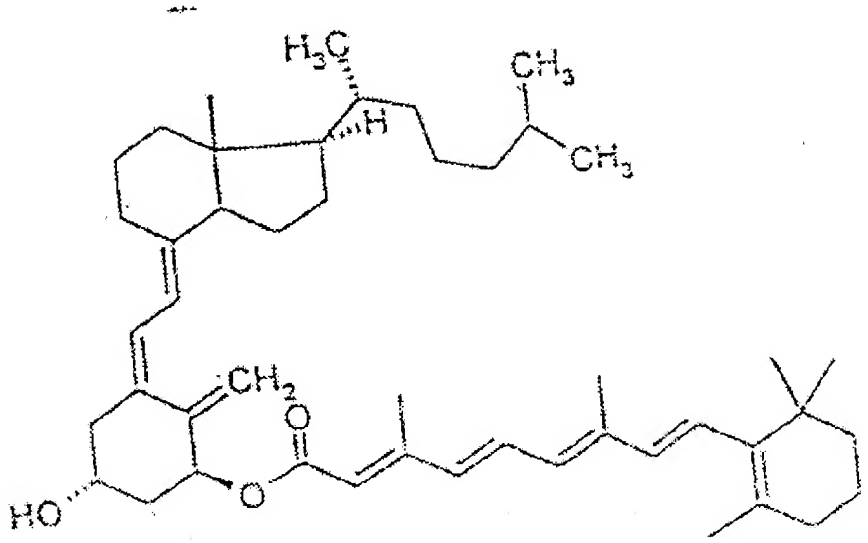
(QV)



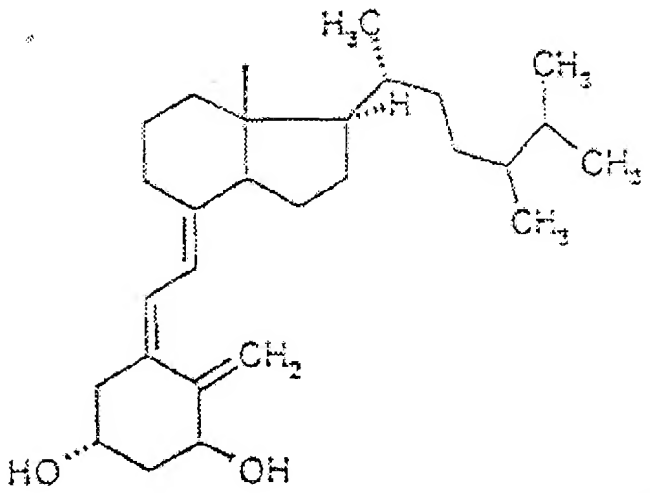
(QVI)



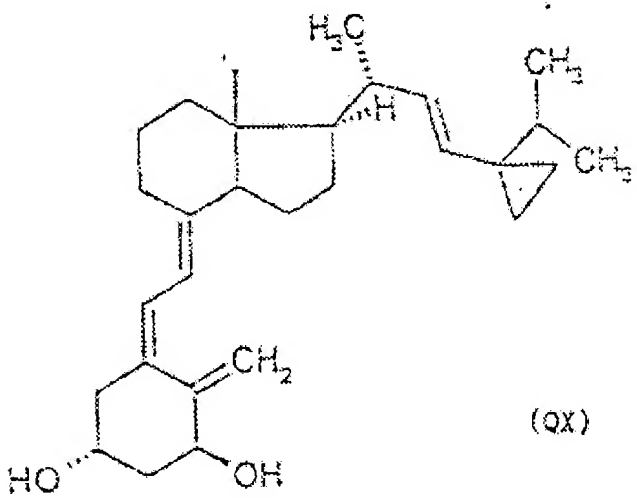
(QVII)



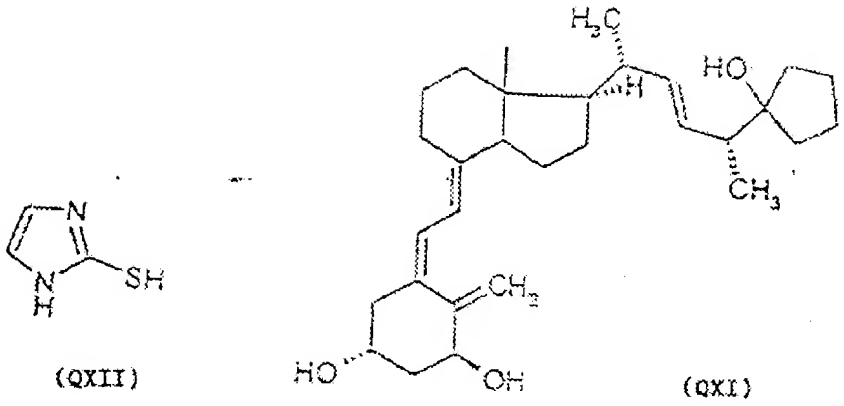
(QVIII)



(QIX)

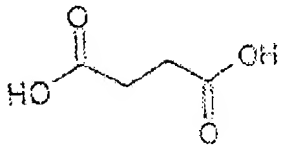


(QX)



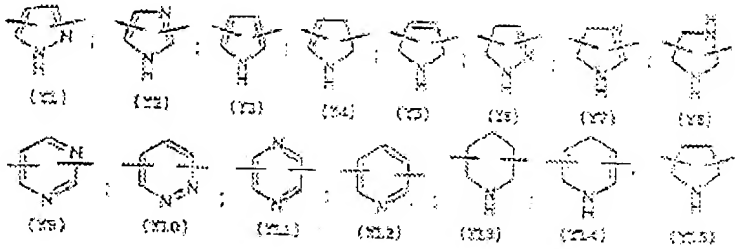
(QXII) (QXI)

succinic acid (RI)



(RI)

3. (Amended) Compounds according to claim 1, wherein in formula (III) Y^3 is selected from the following:



CLAIM 4 (ORIGINAL)

4. Compounds according to claim 3, wherein Y^3 is Y12 (pyridyl), substituted in positions 2 and 6.

5. (Amended) Compounds according to claim 1 wherein the precursor drugs of the compounds of formula (I) and (II) are selected from the following: anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant-mucolytic drugs, antiasthmatic-antiallergic, antihistaminic drugs, ACE-inhibitors, beta-blockers, antithrombotic drugs, vasodilators, antidiabetic, antitumoral, antiulcer, antihyperlipidemic, antibiotic, antiviral drugs, bony reabsorption inhibitors, antidementia drugs.

CLAIM 6 (ORIGINAL)

6. Compounds according to claim 5, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: aceclofenac, acemetacin, acetyl-salicylic acid, 5-aminoacetylsalicylic acid, alclofenac,

7. (Amended) Compounds according to claim 5, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: acetylsalicylic acid,

5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac,

flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen,

ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam,

mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac,

suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen,

buprenorphine, butorphanol, capsaicin, diacereine, dihydrocodeine, ethylmorphine,

eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan,

tramadol, actarit;

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol,

clenbuterol, diphylline, etophylline, fenoterol, ipratropium bromide, metaproterenol,

oxybutynin pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-yl methyl) acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaiacol, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

antiulcer drugs: cimetidine, omeprazole, pantoprazole;

antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

antibiotics drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine,

isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: aciclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid.

8. (Amended) Compounds or salts, or their compositions according to claim 1 for use as drugs;

provided that in the compounds of formula (I) the following drugs under the following conditions are excluded:

- when bo = 0 and C = -T_C-Y_0-, wherein the free valence of Y_0 is saturated as above indicated, s = 2, the drug of formula A = R—T_1-, as above defined, has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE-inhibitors), prostaglandins;
- when bo = 0 and C = -T_C-Y-, wherein the free valence of Y is saturated as above indicated, and s = 2, the drugs of formula A = R—T_1- belonging to the class of non steroid anti-inflammatory drugs.

9. (Amended) Use of compounds or salts, or compositions thereof according to claim 1 for the preparation of drugs for the therapeutic stress-oxidative application

- when bo = 0 and C = -T_C-Y_0-, wherein the free valence of Y_0 is saturated as above indicated, s = 2, the drugs of formula A = R—T_1- can be drugs for use in incontinence, antithrombotic drugs, prostaglandin;

- when bo = 0, C = -T_C-Y-, wherein the free valence of Y is saturated as above indicated, s = 2, the drugs can be non steroid anti-inflammatory drugs.

10. (Amended) Pharmaceutical formulations containing as active principle the compounds or their salts of claim 1.